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Pharmacological Effect of α-Glucosidase Inhibitor Voglibose in a Novel Obese Diabetic Model

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Authors' contributions

This work was carried out in collaboration between all authors. Authors TO, MS and TY designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors TO, YK and KM managed the analyses of the study, and performed the statistical analyses. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aim: This study was conducted to investigate the preventive or therapeutic effect of α-glucosidase inhibitor voglibose in a new model rat, Spontaneously Diabetic Torii-*Lepr*^{fa} (SDT fatty) rat, which is a novel type 2 diabetic rat showing obesity, hyperglycemia and

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hyperlipidemia from a young age.
Place and Duration of Study: Niigata University and JT Central Pharmaceutical Research Institute, between January and August 2011.
Methodology: The present study was designed to the preventive and therapeutic effect of voglibose by administering (0.3, 1 mg/kg) voglibose as a dietary admixture to SDT fatty rats from 5 to 11 and 14 to 20 weeks of age, respectively.
Results: In the examination of preventive effect, the obtained biochemical results show that voglibose decrease glucose level significantly in dose-dependent manner within 5-11 weeks of age. In voglibose-treated rats at 11 weeks of age, the histopathological pancreatic changes, such as vacuolation and irregular boundaries in islets, were improved. On the other hand, in the examination of therapeutic effect, voglibose improved the hyperglycemia only at a dose of 1 mg/kg within 16-20 weeks of age.
Conclusion: Voglibose showed both preventive and therapeutic effects for diabetes in female SDT fatty rats. The SDT fatty rat is a useful model for development of anti-diabetic agents.

Keywords: α-Glucosidase inhibitor; diabetic rat; SDT fatty rat.

1. INTRODUCTION

Diabetes mellitus has become a global health problem, and the incidence of the disease is increasing rapidly all over the world [1]. Furthermore, the prevalence of obesity is increasing worldwide at an alarming rate [2]. Diabetic animal models play critical roles in the elucidation of the mechanism of diabetes mellitus and the development of novel drugs as treatments [3,4].

Spontaneously Diabetic Torii-*Lepr*^{fa} (SDT fatty) rat, established by introducing the *fa* allele of the Zucker fatty rat into the SDT rat genome, represents a new model of obese type 2 diabetes [5]. SDT fatty rats of both sexes exhibited hyperphagia and obesity after weaning, and the hyperglycemia and the hyperlipidemia were observed from a young age, 4-6 weeks [3,6,7]. Moreover, the blood pressure in SDT fatty rats increased after 8 weeks of age [8,9]. The female SDT fatty rat has the potential to become an important animal model of obese type 2 diabetes, especially for women, for which few models currently exist [6].

α-Glucosidase inhibitors such as acarbose and voglibose are considered to act in the small intestine by competitively inhibiting the breakdown of carbohydrates, thereby specifically reducing postprandial glucose excursion. They are widely used to reduce postprandial hyperglycemia and hyperinsulinemia in diabetic patients [10]. Also, it is reported that α-glucosidase inhibitors can prevent or delay the development of diabetes in high-risk individuals with impaired glucose tolerance [11,12].

In this study, voglibose was administered to female SDT fatty rats under preventive and therapeutic conditions, and the effects of voglibose were investigated.

2. MATERIALS AND METHODS

2.1 Animals

Female SDT fatty rats were kindly given from JT (Tokyo, Japan). Age-matched Sprague-Dawley (SD) rats were used as control animals. SD rats were purchased from CLEA Japan

Inc. (Tokyo, Japan). Rats were housed in suspended bracket cages and given a standard laboratory diet (CRF-1, Oriental yeast co., ltd. Tokyo, Japan) and water *ad libitum* in a controlled room for temperature, humidity and lightning.

2.2 Preventive Effects of Voglibose

Voglibose (0.3, 1 mg/kg) in a dietary mixture was administered to SDT fatty rats from 5 to 11 weeks of age (n=5). Body weights, food intake, and non-fasted serum biochemical parameters, such as glucose, insulin, triglyceride (TG), and total cholesterol (TC) levels, were examined every two weeks. The glucose, TG and TC levels were measured using commercial kits (Roche Diagnostics, Basel, Switzerland) and an automatic analyzer (Hitachi, Tokyo, Japan). Serum insulin level was measured with a rat-insulin enzyme-linked immunosorbent assay (ELISA) kit (Morinaga Institute of Biological Science, Yokohama, Japan). These serum biochemical parameters were measured in the same manner as in our previous studies [6,7]. Necropsy was performed at 11 weeks of age. The pancreas was fixed in 10% neutral buffered formalin. After resection, the tissue was paraffin-embedded by standard techniques and thin-sectioned (3 to 5 µm). The sections were stained with hematoxylin and eosin (HE).

2.3 Therapeutic Effects of Voglibose

Voglibose (0.3, 1 mg/kg) in a dietary mixture was administered to SDT fatty rats from 14 to 20 weeks of age (n=5). Body weights, food intake, and non-fasted serum biochemical parameters, such as glucose, insulin, TG, and total TC levels, were examined every two weeks.

2.4 Statistical Analysis

Results of biological parameters were expressed as the mean ± standard deviation. A statistical analysis of differences between mean values in control group (SDT fatty rats) and voglibose-treatment group was performed with One-way analysis of variance (ANOVA) followed by Dunnett's two-tailed test. A statistical analysis of differences between mean values in control group (SDT fatty rats) and SD rats was performed using the F-test, followed by the Student's t-test or Aspin-Welch's t-test. Differences were defined as significant at $p < 0.05$.

3. RESULTS

3.1 Preventive Effects of Voglibose

Preventive effects of voglibose in female SDT fatty rats are shown in Fig. 1. Serum glucose levels in female SDT fatty rats were elevated from 7 weeks of age as compared with those in female SD rats, and the increase was sustained until 11 weeks of age. Voglibose inhibited the hyperglycemia dose-dependently as compared with those in the control group (Control group, 566.0 ± 173.0 mg/dl; Voglibose 0.3 mg/kg group, 263.0 ± 200.8 mg/dl; Voglibose 1 mg/kg group, 156.6 ± 26.5 mg/dl, at 11 weeks of age), and the voglibose 1 mg/kg significantly prevented the incidence of diabetes mellitus during the experimental period (Fig. 1C). Hyperphagia was observed in female SDT fatty rats, and voglibose suppressed the hyperphagia dose-dependently (Fig. 1B). Serum non-fasted TG levels in female SDT fatty rats were elevated from 7 to 11 weeks of age as compared with those in female SD rats. Voglibose inhibited the hypertriglyceridemia dose-dependently from 7 to 9 weeks of age (Fig. 1E). Increases of body weight, serum non-fasted insulin, and TC levels were observed in female SDT fatty rats, but voglibose treatment did not affect these parameters (Figs. 1A, D

and F). In pancreas of female SDT fatty rats, histopathological abnormalities, such as irregular boundaries and vacuolation in islets, were observed. Those changes in pancreas were inhibited by chronic treatment of voglibose (Fig. 2).

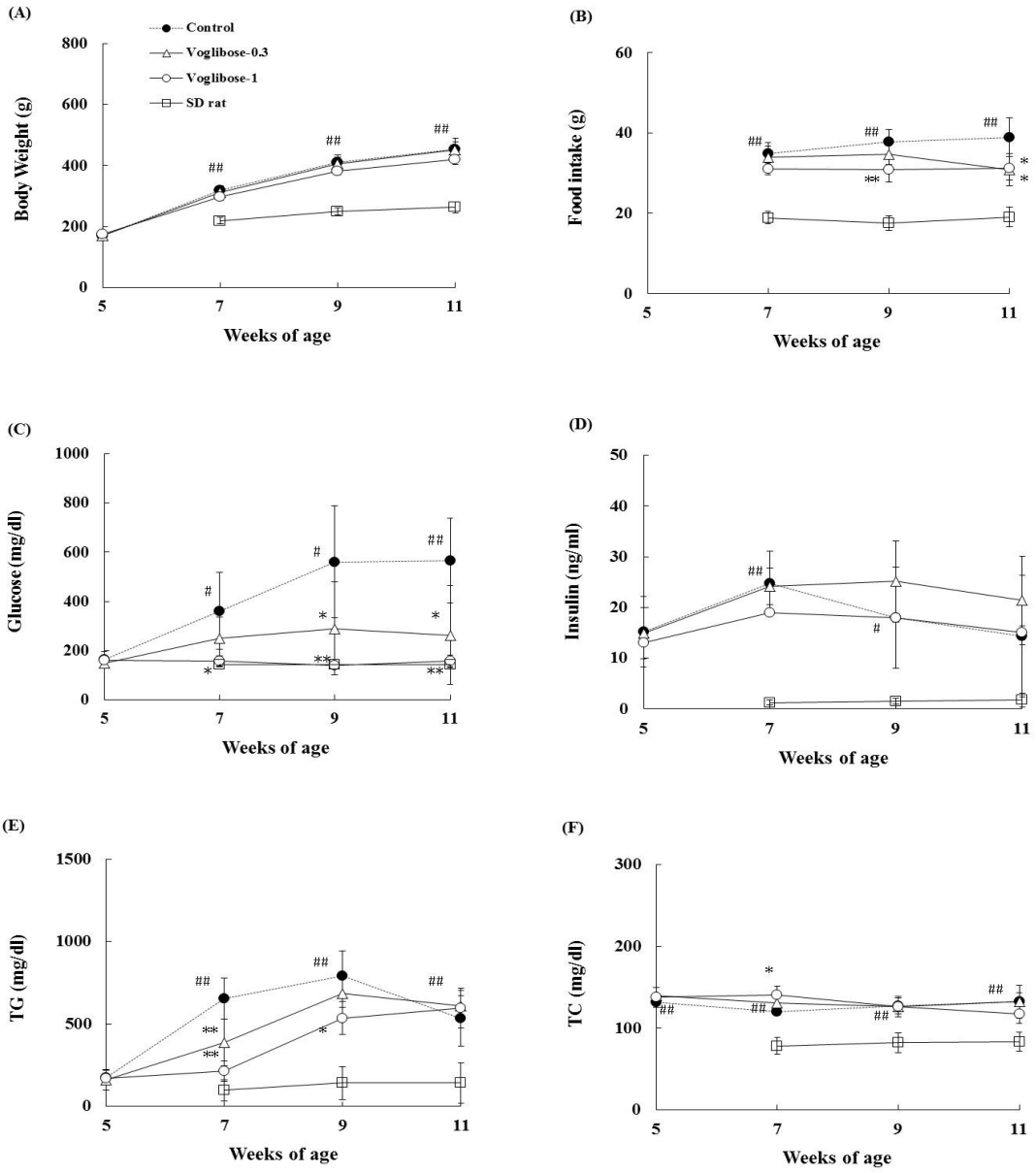

Fig. 1. Effects on body weight (A), food intake (B), and serum glucose (C), insulin (D), TG (E) and TC (F) levels in SDT fatty rats with preventive treatment of voglibose. Data represent mean ± standard deviation (n=5). * p<0.05, **p<0.01; significantly different from the control. #p<0.05, ##p<0.01; significantly different from SD rat

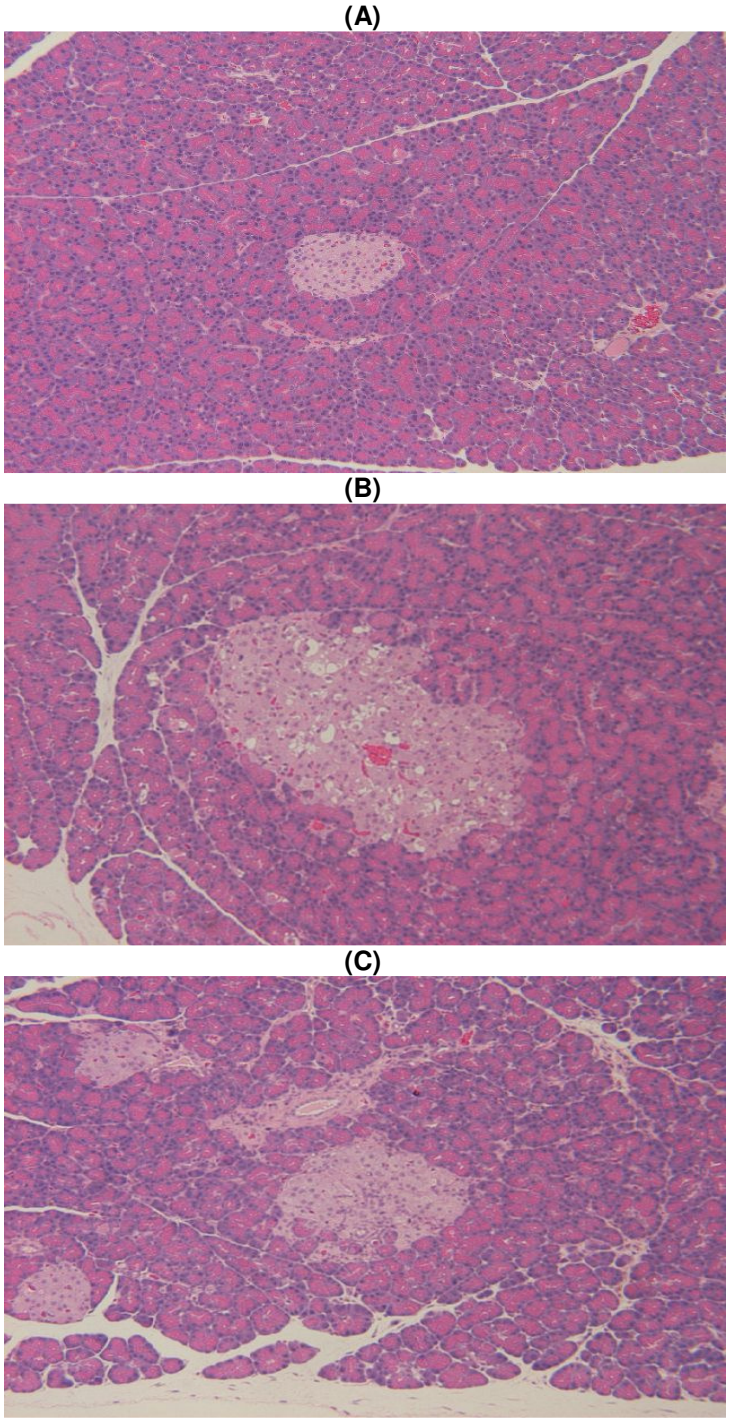

Fig. 2. Histopathological analysis of pancreas.(A) SD rat at 20 weeks of age, (B) SDT fatty rat at 11 weeks of age, and (C) Voglibose-treated SDT fatty rat. Original magnification x 200.HE stain

3.2 Therapeutic Effects of Voglibose

Therapeutic effects of voglibose in female SDT fatty rats are shown in Fig. 3. Serum glucose levels in the SDT fatty rats were elevated at a starting point of the experiment (SDT fatty rat, 734.6 ± 65.8 mg/dl; SD rat, 131.4 ± 3.6 mg/dl), and the elevation was sustained during the experimental period. Voglibose 1 mg/kg showed a significant decrease from 16 to 20 weeks of age (Control group, 649.6 ± 91.5 mg/dl; Voglibose 1 mg/kg group, 226.2 ± 134.7 mg/dl, at 20 weeks of age) (Fig. 3C). Food intake in female SDT fatty rats increased at 18 and 20 weeks of age, as compared with those in SD rats. Voglibose inhibited the increase dose-dependently at 20 weeks of age (Control group, 38.2±5.0g; Voglibose0.3 mg/kg group, 31.8±2.2g; Voglibose 1 mg/kg group, 29.4±4.1g) (Fig. 3B). Voglibose treatment did not affect the body weight, serum non-fasted insulin, or serum non-fasted lipids levels (Figs. 3A, D, E, and F).

4. DISCUSSION

A preventive effect of α-glucosidase inhibitor is reported in other diabetic models. Acarbose can delay, prevent, or reverse the metabolic and histopathological changes in genetically obese and diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats [13]. In SHR/N-cp rats fed a sucrose diet, ingestion of acarbose showed a decrease of total food intake [14]. On the other hand, in OLETF rats, acarbose treatment showed an increase of food intake [13]. In this study using SDT fatty rats, the decrease of food intake (Fig. 1B) is considered to be a factor for showing the preventive effects of voglibose. In OLETF rats, acarbose-treatment inhibited the increase of body weight, TG, and TC levels [13], but the SDT fatty rats with voglibose-treatment did not show the decreases of body weight, TG, and TC levels (Figs. 1A, D, and F).

Therapeutic effects of α-glucosidase inhibitors, voglibose and acarbose, were investigated in other diabetic models. When voglibose was administered to GK rats from 12 to 36 weeks of age, fasting blood, non-fasting blood, and hemoglobin A1c (HbA1c) levels were significantly decreased [15]. Moreover, chronic treatment with acarbose improved the hyperglycemia in Long-Evans Tokushima Otsuka (LETO) rats and obese diabetic Wistar rats [16,17]. It is considered that a chronic treatment with α-glucosidase inhibitor induced the sufficient glycemic control by daily inhibition of postprandial hyperglycemia. Preventive treatment of voglibose showed the histological improvement in pancreas of SDT fatty rats (Fig. 2). In the therapeutic study, the similar morphological improvements in pancreas were observed in voglibose-treatment (data not shown). It is reported that treatment with voglibose enhances glucagon-like peptide-1 (GLP-1) secretion [18,19]. GLP-1 is reported to stimulate proliferation, enhance differentiation and inhibit apoptosis of beta-cells [20,21]. Enhancement of incretin hormone secretion might be related with the histological improvements in pancreas after voglibose treatment. In further study, functional assays by glucose tolerance test or insulin tolerance test and quantitative evaluation, such as determination of pancreatic beta cell mass and insulin content, are indispensable in the SDT fatty rats after treatment of anti-diabetic drugs.

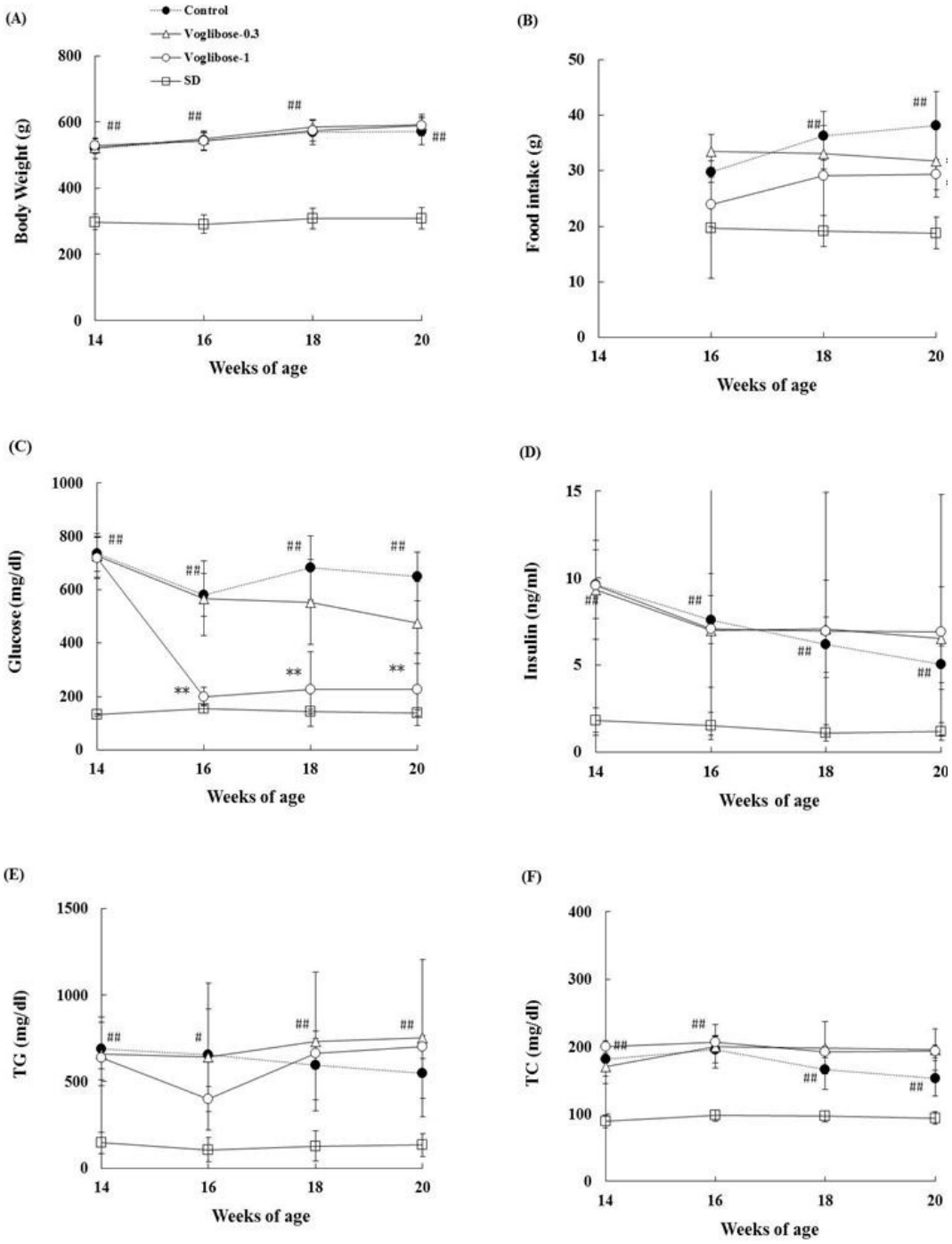

Fig. 3. Effects on body weight (A), food intake (B), and serum glucose (C), insulin (D), TG (E) and TC (F) levels in SDT fatty rats with therapeutic treatment of voglibose. Data represent mean ± standard deviation (n=5). * p<0.05, **p<0.01; significantly different from the control. #p<0.05, ##p<0.01; significantly different from SD rat

5. CONCLUSION

Voglibose showed both preventive and therapeutic effects for diabetes in female SDT fatty rats. The SDT fatty rat is a useful model for discovery and development of α-glucosidase inhibitors.

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

The authors report no conflicts of interest.

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